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White Matter Microstructure and the General Psychopathology Factor in Children

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Objective: Co-occurrence of behavioral and emotional problems in childhood is widespread, and previous studies have suggested that this reflects vulnerability to experience a range of psychiatric problems, often termed a general psychopathology factor. However, the neurobiological substrate of this general factor is not well understood. We tested the hypothesis that lower overall white matter microstructure is associated with higher levels of the general psychopathology factor in children and less with specific factors.

Method: Global white matter microstructure at age 10 years was related to general and specific psychopathology factors. These factors were estimated using a latent bifactor model with multiple informants and instruments between ages 6 and 10 years in 3,030 children from the population-based birth cohort Generation R. The association of global white matter microstructure and the psychopathology factors was examined with a structural equation model adjusted for sex, age at scan, age at psychopathology assessment, parental education/income, and genetic ancestry.

Results: A 1-SD increase of the global white matter factor was associated with a $\beta = -0.07$SD (standard error [SE] = 0.02, $p < .01$) decrease in general psychopathology. In contrast, a 1-SD increase of white matter microstructure predicted an increase of $\beta = +0.07$ SD (SE = 0.03, $p < .01$) specific externalizing factor levels. No association was found with the specific internalizing and specific attention factor.

Conclusion: The results suggest that general psychopathology in childhood is related to white matter structure across the brain and not only to specific tracts. Taking into account general psychopathology may also help reveal neurobiological mechanisms behind specific symptoms that are otherwise obscured by comorbidity.

Key words: magnetic resonance imaging, externalizing disorder, internalizing disorder, attention, structural equation modeling

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Child psychological problems are commonly grouped into behavioral/externalizing and emotional/internalizing problems based on the observation that symptoms within a given domain often co-occur. Nonetheless, even across these broadly defined domains, symptoms correlate substantially.[1,2] Likewise, categorically defined psychiatric disorders co-occur above chance level.[3,4] In recent years, studies in children,[5–7] adolescents,[8,9] and adults[10,11] have suggested that this broadly shared variance can be described by a latent construct underlying all psychiatric problems: a general psychopathology factor. These studies support the hypothesis that co-occurence of psychiatric problems is explained by both a general propensity to have any problem and a specific propensity to display characteristics of a certain psychopathology domain.[12]

The question arises whether this higher-order structure of psychopathology is mirrored in the brain.[12] Zald and Lahey[13] propose a framework in which some brain features underlie the risk to experience any psychiatric problems, whereas other neural circuits are linked to the occurrence of specific symptoms. Possibly, global brain characteristics reflect a nonspecific psychopathology risk. White matter microstructure, the backbone of efficient neural communication, is a possible candidate substrate.

White matter microstructure encompasses several neural characteristics important for providing connectivity, such as axonal properties and degree of myelination. These characteristics are determined by genetic and environmental factors.[14] White matter differences across several regions were associated with psychological and psychiatric outcomes, such as IQ,[15] early-onset schizophrenia and bipolar disorder,[16] attention-deficit/hyperactivity disorder (ADHD),[17] anxiety, and depression.[18,19] Most studies tested only the effects of specific tracts. However, given the diversity of tracts identified,

the question arises whether these associations represent effects of global variation of white matter across the brain. Although the literature is sparse, studies examining whole-brain metrics demonstrated that lower global white matter microstructure is associated with lower cognitive abilities in children,[15] increased odds of depression in adulthood,[19] and more internalizing problems in children born preterm.[20]

These studies used traditional definitions of single disorders/domains and did not distinguish general and specific associations. The use of a latent general psychopathology factor may help characterize whether white matter microstructure is associated with general vulnerability to psychopathology. In parallel, specific psychopathology factors that are not correlated with the general psychopathology factor can be tested. A study in university students estimated a latent general psychopathology factor and found associations with lower white matter integrity in the pons, lemniscus and peduncle.[21] However, studies investigating global white matter and specific psychopathology factors are missing.

Against this background, we hypothesized that lower global white matter microstructure across the brain is associated with higher levels of the general psychopathology factor and less with specific psychopathology factors. To test this hypothesis, we measured global white matter microstructure using diffusion tensor imaging (DTI) in 10-year-old children participating in the Generation R Study (GenR), a population-based cohort. Global white matter microstructure was quantified as latent construct, reflecting white matter microstructure of 12 measured tracts. We repeatedly assessed common psychological problems from ages 6 to 10 years using mother, father, teacher, and child reports, and estimated general and specific psychopathology factors.

METHOD

Participants and Ethical Considerations

This study was embedded in GenR,[22,23] a population-based birth cohort. All parents gave informed consent for their children's participation. GenR is conducted in accordance with the Declaration of Helsinki. Study protocols were approved by the Ethics Committee of the Erasmus Medical Center.

Usable DTI scans were available for 3,050 children. At least one psychological problem subscale was available for 3,030 children. All results are based on this sample of 3,030 children, except for the results of the tract-based spatial statistics (TBSS)[24] analysis (n = 2,996) (Figure S1, available online). Descriptive statistics can be found in Table 1. A full method description can be found in Supplement 1, available online. The main model results can be reproduced using the covariance matrix and scripts in Supplement 2 and Supplement 3, available online. To ensure participant privacy and compliance with Dutch law, individual-level data cannot be made publicly available without explicit informed consent, which is not available. For new analyses or individual-level data access, please contact Generation R data management (datamanagementgenr@erasmusmc.nl) and the corresponding author.

TABLE 1 Demographics of Analysis Sample (N = 3,030)

Characteristic	n_{obs}	%
Sex	3,030	
Girls	1,528	50.4
Household income	2,541	
<2,800€	835	32.9
2,800−4,800€	1,079	42.5
>4,800€	627	24.7
Maternal education	2,659	
No or Primary	86	3.2
Secondary	908	34.1
Higher	1,665	62.6
Paternal education	2,456	
No or Primary	109	4.4
Secondary	833	33.9
Higher	1,514	61.6
Genetic ancestry	1,889	
Northwestern European	1,136	60.1
Child IQ	n_{obs}	Mean (SD)
Score	2,640	103.3 (14.8)

Note: n_{obs} = observed sample size.

Measures

Child Psychological Problems. We used the Child Behavior Checklist (CBCL) $1\frac{1}{2}$ −5 years[25] to assess child behavioral problems at age 6 years (mean = 5.9, SD = 0.3) and the CBCL 6−18[26] at age 10 years (mean = 10, SD = 0.3). At the age of 6 years, questionnaires were completed by the primary caregiver (92% mothers). At age 10 years, the questionnaire was filled in by the mother and father separately. Teachers assessed children at age 7 years (mean = 6.5, SD = 1.1) with the Teacher's Rating Form 6−18.[26] At age 6 years (mean = 6.0, SD = 0.4), we conducted the Berkeley Puppet Interview,[27] a semi-structured interactive child interview. At age 10 years (mean = 9.8, SD = 0.3), the children rated their symptoms using the Brief Problem Monitor[28] plus thought problem items.

Diffusion Tensor Imaging. Children underwent DTI at age 10 years (mean = 10.1, SD = 0.6). Magnetic resonance imaging (MRI) scans were performed using a 3T General

Electric scanner with an 8-channel head coil. DTI consisted of a 35-direction echo planar imaging sequence (T_R = 12,500 milliseconds, T_E = 72 milliseconds, field of view (FoV) = 240 mm × 240 mm, acquisition matrix = 120 × 120, slice thickness = 2 mm, slice number = 65, Asset Acceleration Factor = 2, b = 900 s/mm^2, 3 b = 0 images). We computed fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).[29] Connectivity distributions for 12 large, well-defined, widely reported fiber bundles were derived with probabilistic fiber tractography.[30,31] For TBSS analyses, the DTI images were registered to a study-specific and age-appropriate template.[32]

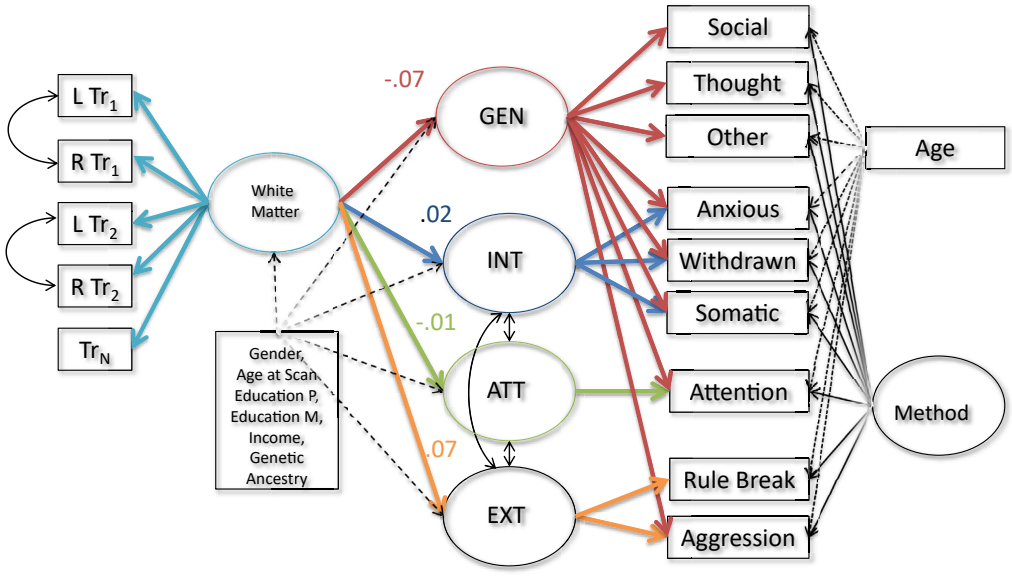
Measures of IQ, School Performance, Temperament, Happiness, and Parental Psychopathology. We assessed nonverbal IQ with the Snijder-Oomen nonverbal intelligence test at age 6 years.[33] At the same age, we measured temperamental dimensions with the Children's Behavior Questionnaire (Very-Short-Form) (CBQ), a parent-rated questionnaire.[34] School performance was assessed by the Cito, a standardized language and mathematics examination at the end of primary school.[35] Happiness was measured by asking the parents at age 10: "How often was your child happy in the past 4 weeks?" Parental psychopathology was assessed with the Brief Symptom Inventory.[36]

Statistical Analysis

We used a structural equation model to associate global white matter microstructure with general and specific factors of psychopathology (Figure 1). All models were fitted in R 3.4.1[37] with Lavaan 0.5-23.11097.[38] We used maximum likelihood with robust standard errors to account for multivariate nonnormality. Child psychological problems between ages 6 and 10 years were jointly analyzed to ensure convergence and reliable estimation of factors. CBCL total scores as assessed by mothers were moderately stable between 6 and 10 years (r = 0.59).

General Psychopathology Factor. The general psychopathology factor was specified to underlie all problem subscales from all instruments and time-points (Table S1, available online). The subscales were specified to load on one of the specific internalizing, externalizing, or attention factors defined on the basis of the assessment scales. Specific psychopathology factors were allowed to correlate among each other, but not with the general psychopathology factor. The specific factors thus represent covariance among subscales not explained by a general propensity for psychiatric problems. As such, the specific factors differ distinctly from the observed broadband scales; for example, the specific externalizing and internalizing factors do not correlate positively (r = −0.36, SE = 0.04, p < .01) because the shared variance is captured by the general factor.[11] The

FIGURE 1 Abbreviated Path Diagram of the Main Analysis Model



Note: All latent variables (oval shape) are included. Observed variables (square) from the Child Behavior Checklist (CBCL) at age 10 years by a single informant are displayed as an example. Observed variables from other instruments and informants, as well as specific tracts were omitted. Numbers displayed are standardized regression coefficients. ATT = attention; Education M = maternal education; Education P = paternal education; EXT = externalizing; GEN = general psychopathology; INT = internalizing; L Tr = left tract; R Tr = right tract; White matter = global white matter integrity. Please note color figures are available online.

same holds for the specific attention−internalizing correlation ($r = -0.47$, SE = 0.03, $p < .01$). The specific attention and externalizing factors did not correlate ($r = +0.06$, SE = 0.03, $p = .06$). It is important to note that we included additional method factors, which capture the shared variance unique to an informant of the child.

The latent factor structure was based on previous GenR and other studies.[6,8,11,12] We performed several additional analyses. First, we tested models without a general psychopathology factor (Table S2, available online) and observed a substantial fit decrease. Also, we present associations from a three-factor model (internalizing, externalizing, and attention) without the general psychopathology factor as comparison. In this analysis, we removed the method factors, as they cause the psychopathology factors to behave as specific factors. All psychopathology factors showed expected high correlations (0.71 between internalizing and externalizing, 0.75 between attention and externalizing, and 0.55 between attention and internalizing). Next, we tested a second-order model, in which the psychopathology factors load on a second-order general psychopathology factor. We also tested associations with maternally rated CBCL sum-scores at age 10 years (total problems, externalizing, internalizing, attention). To mimic the specific factors in such an analysis, we controlled for total problems in an alternative model. Second, we explored four models with IQ at age 6 years, temperament (negative affectivity, surgency, and effortful control measured at age 6 with CBQ), school performance at the end of primary school, and happiness as predictors of the psychopathology factors. Surgency here refers to a construct related to extraversion and describes high amounts of activity and approach behaviors.[6] Third, we performed sensitivity analyses adjusted for total intracranial volume and the number of motion-affected volumes to investigate potential confounding.[39]

Global White Matter Microstructure Factor. The global white matter microstructure factor was estimated using the mean FA values of 12 white matter tracts as indicators (Table S3, available online). FA describes how elongated the ellipsoid shape of a diffusion pattern is, with higher values suggesting higher white matter integrity. This model was based on previous GenR studies.[15,31] We included the corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus of each hemisphere separately in the model. Some children had very low or high FA values 4 SDs above or below the mean. To test in a sensitivity analysis how influential these values were, we winsorized extreme values, defined at three times the interquartile range, per white matter tract. It can be also helpful to examine diffusivity perpendicular to the main axis of diffusion (RD) or alongside it (AD). Higher RD and lower AD are associated with less white matter microstructure. Thus, to better understand results from the FA model, we also estimated global white matter variables based on RD, AD, and MD (the average diffusivity in any direction).

Structural Paths. The general and specific psychopathology factors were each simultaneously regressed on the global white matter factor using FA values to test the associations between white matter microstructure and psychopathology. Figure 1 illustrates the main model used to test the main hypothesis. All other models are for exploratory purposes to interpret the results of the main model. We adjusted all models for several potential confounders in the model (sex, scan/assessment age, maternal and paternal education, income, and genetic ancestry). All subsequent coefficients are reported as standardized. We explored whether associations were specific to psychopathology by including child IQ as a covariate. In addition, we controlled for maternal/paternal psychopathology (interpersonal sensitivity, depression, anxiety, and hostility) to explore whether the association was independent of parental characteristics. We also performed a sensitivity analysis of the main model additionally adjusted for body mass index.[40] We tested for nonlinear associations, by fitting a standard regression model with estimated factor scores analogous to the main model, but with the addition of a squared term for the global white matter factor score. We reran the main model with global white matter factor based on MD, RD, and AD. p Values were adjusted for multiple testing of four outcomes using the false discovery rate (FDR).

Follow-up Analyses. We ran follow-up analyses to investigate the individual contribution of each individual white matter tract by replacing global white matter with the observed FA of single tracts. We tested each tract in separate models, as well as mutually adjusted. In these exploratory follow-up analyses, we computed FDR adjusted p values for 12 tracts per 4 outcomes (48 tests).

In follow-up analyses, we tested individual voxels ($n_{voxels} = 9{,}272$) in a TBSS analysis for DTI scalars and outcomes, which showed a significant association on a global level (see Supplement 1, available online).

We also attempted to replicate previously reported associations in the pons, lemniscus, and peduncle.[21] For the pons, we extracted the average FA values within a 4-mm sphere around three coordinates (left pons: x = 12,−39, −42; right pons 1: x = 5,−37, −35; right pons 2: x = −5, −37, −35). For the left/right lemniscus and medial peduncle, we extracted the average FA of the tract, as

described above. Replication models were identical to the main model, with the regions either replacing the global white matter factor or jointly estimated to test for independent effects.

To test to which degree potential associations between white matter and the psychopathology factors represent associations with temperament, we regressed the temperamental scales on global white matter adjusted for the same covariates as the main model.

Measurement Invariance. We tested the assumption that the latent constructs and the associations between them are identical across sex, ancestry and socioeconomic status by performing measurement invariance analyses (see Supplement 1, available online).[41-43]

RESULTS

Latent Variable Loadings

The FA score of all white matter tracts loaded on global white matter microstructure. Loadings ranged from 0.41 (cingulum bundle) to 0.74 (superior longitudinal fasciculus) (Table S3, available online). Differences in loadings between left and right hemispheres were small; thus both hemispheres contributed equally to the global white matter construct.

All problem subscales had statistically significant loadings on the general psychopathology factor. Most loadings were moderate to high [0.30–0.70], some teacher and child self-report loadings at age 6 to 7 years were below 0.20 (Table S1, available online). The general psychopathology factor model had a better fit than alternative models (Table S2, available online). The loadings of the problem subscales on the specific factors tended to be lower than on the general factor.

IQ, School Performance, Temperament, and Happiness

Children with a higher IQ had lower general psychopathology levels ($\beta = -0.12$, SE = 0.02, $p < .01$) and less specific attention problems ($\beta = -0.15$, SE = 0.02, $p < .01$), but not more specific externalizing and internalizing problems (Table 2). Those who performed well at school had lower general psychopathology levels ($\beta = -0.12$, SE = 0.02, $p < .01$), less specific externalizing problems ($\beta = -0.06$, SE = 0.03, $p = .02$), and less specific attention problems ($\beta = -0.31$, SE = 0.02, $p < .01$). Children who scored high on negative affectivity had particularly high levels of the general psychopathology factor ($\beta = +0.40$, SE = 0.02, $p < .01$). Associations of the negative affectivity score with the specific psychopathology factors were weaker. A different pattern of associations was observed for surgency. Children with higher levels of surgency had lower specific internalizing levels ($\beta = -0.50$, SE = 0.02, $p < .01$) and higher specific externalizing levels ($\beta = +0.20$, SE = 0.02, $p < .01$). Associations of effortful control with all factors were weak. Happier children had lower levels of general psychopathology ($\beta = -0.23$, SE = 0.02, $p < .01$), lower levels of specific externalizing levels ($\beta = -0.12$, SE = 0.02, $p < .01$), and lower levels of specific internalizing levels ($\beta = -0.15$, SE = 0.03, $p < .01$). No temperamental scale was associated with global

TABLE 2 Psychopathology Factors Regressed on IQ and Temperament

		Factor											
		General			Specific ext			Specific int			Specific att		
Predictor	n_{obs}	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*P*
Child IQ	2,640	−0.12	0.02	<.01	−0.05	0.03	.06	0.03	.03	.p1	−0.15	.02	<.01
School performance	1,311	−0.12	0.02	<.01	−0.04	0.01	<.01	−0.00	0.01	.73	−0.21	0.02	<.01
Negative affectivity	2,329	0.40	0.02	<.01	0.12	0.03	<.01	0.15	0.03	<.01	−0.06	0.02	<.01
Surgency	2,326	0.11	0.02	<.01	0.20	0.02	<.01	−0.50	0.02	<.01	0.18	0.02	<.01
Effortful control	2,321	−0.13	0.02	<.01	−0.10	0.02	<.01	0.06	0.02	<.01	−0.17	0.02	<.01
Happiness	2,117	−0.23	0.02	<.01	−0.12	0.02	<.01	−0.15	0.03	<.01	0.05	0.02	.03
3-factor model			—		Externalizing			Internalizing			Attention		
Child IQ	2,640	—	—	—	−0.03	0.01	<.01	0.01	0.01	.54	−0.11	0.02	<.01
School performance	1,311	—	—	—	−0.12	0.03	<.01	0.00	0.03	.88	−0.33	0.02	<.01
Negative affectivity	2,329	—	—	—	0.10	0.01	<.01	0.11	0.01	<.01	−0.01	0.01	.59
Surgency	2,326	—	—	—	0.10	0.01	<.01	−0.18	0.01	<.01	0.14	0.01	<.01
Effortful control	2,321	—	—	—	−0.06	0.01	<.01	0.00	0.01	.96	−0.13	0.02	<.01
Happiness	2,117	—	—	—	−0.09	0.01	<.01	−0.07	0.01	<.01	0.01	0.01	.61

Note: *Att = attention; analysis n = 3,030; Ext = externalizing, Int = internalizing; β = standardized regression coefficient, n_{obs} = observed sample size; SE = standard error.*

white matter (negative affectivity, $\beta = -0.02$, SE = 0.02, $p = .37$; surgency, $\beta = 0.00$, SE = 0.02, $p = .83$; effortful control, $\beta = -0.01$, SE = 0.02, $p = .52$).

Psychopathology Factors Associations With White Matter Microstructure

Table 3 summarizes the results of the global white matter microstructure analyses. Global white matter did not associate with maternally rated CBCL sum-scores. In the three-factor model not including the general factor, an association between white matter microstructure and the traditionally defined externalizing factor was found ($\beta = +0.03$ SD, SE = 0.01, $p = .05$). The externalizing ($\lambda = 0.84$), internalizing ($\lambda = 0.87$), and attention ($\lambda = 0.74$) factors loaded strongly on a second-order general factor, but this did not improve model fit (Table S2, available online). Also, this second-order general psychopathology factor was not associated with matter microstructure ($\beta = 0.02$ SD, SE = 0.01, $p = .05$).

Next, we modeled the general psychopathology factor in a bifactor model with specific psychopathology factors. A 1-SD increase in the global white matter factor was associated with a $\beta = -0.07$SD (SE = 0.02, $p < .01$, q < 0.01) decrease in general psychopathology. In contrast, a 1-SD increase in white matter microstructure predicted an increase of $\beta = +0.07$ SD (SE = 0.03, $p = .01$, q = 0.02) specific externalizing factor levels. Follow-up analyses showed that this association appears to be driven by radial diffusivity ($\beta = -0.07$ SD, SE = 0.03, $p = .01$, q = 0.04), as opposed to axial diffusivity ($\beta = -0.02$SD, SE = 0.03, $p = .39$, q = 0.39). Thus, whereas children with more general psychopathology had lower global white matter microstructure, children with a higher specific externalizing factor had more white matter microstructure. (See Figure S2, available online, for scatter plots based on estimated factor scores.) Winsorizing extreme FA values slightly increased effect sizes to $\beta = +$-0.08SD for general and specific externalizing psychopathology. Quadratic terms of the global white matter factor scores were not significant (Table S4, available online). For both the general factor and the externalizing factor, the associations were largely independent of child IQ, parental psychopathology, body mass index, total intracranial volume, and motion (Table 3). Covariate associations can be found in Table S5, available online. Global white matter was associated with age at scan, ancestry, maternal depression, and IQ. IQ and age showed the strongest positive association ($\beta = +0.12$ and $\beta = +0.15$, respectively) with white matter integrity.

The individual white matter tracts were negatively associated with the general psychopathology factor, with the exception of the cingulum bundle, and positively with the specific externalizing factor (Table S6, available online). The magnitude of associations were mostly lower than those of the global white matter factor. The forceps minor and right superior longitudinal fasciculus were associated with general psychopathology after adjustment for FDR, whereas only the relation of the corticospinal tract with the specific externalizing factor survived such correction. After mutual adjustment, this association was no longer significant, supporting the presence of a substantial global white matter component.

The latent variable models suggest that a global white matter factor based on the FA scalar is negatively associated with the general psychopathology factor and positively with the specific externalizing factor. The results from the voxel-wise analyses were consistent with the global white matter models. For general psychopathology, 1,548 (17%) voxels showed a negative association and 0 (0%) a positive association accounting for multiple testing. We found that 85.9% of these voxels formed a single continuous clusters, which was spread across the whole brain (Table S7, available online, and Figure 2). It is therefore not possible to define this cluster by specific brain regions, though we observed that voxels were especially represented in the left inferior longitudinal fasciculus and left corticospinal tract (Table S8, available online). For the specific externalizing factor, 4,842 (52%) voxels showed a positive association and 0 (0%) a negative. Because the global white matter factor was also associated with the specific externalizing factor when the structural equation models were based on MD and RD, we tested these scalars in TBSS analyses as well. MD values were significant for 5,149 (56%) voxels and RD for 6,282 (68%) with all associations in the negative direction. Among the defined regions, the forceps minor contained the most associated voxels (Table S8, available online). Depending on the scalar, 97.0% (FA), 99.9% (MD) or 99.7% (RD) of significant voxels formed a continuous cluster. As with the general psychopathology factor, the cluster also spread across the whole brain and the global nature was very pronounced (Table S7, available online, and Figure 2).

Measurement Invariance

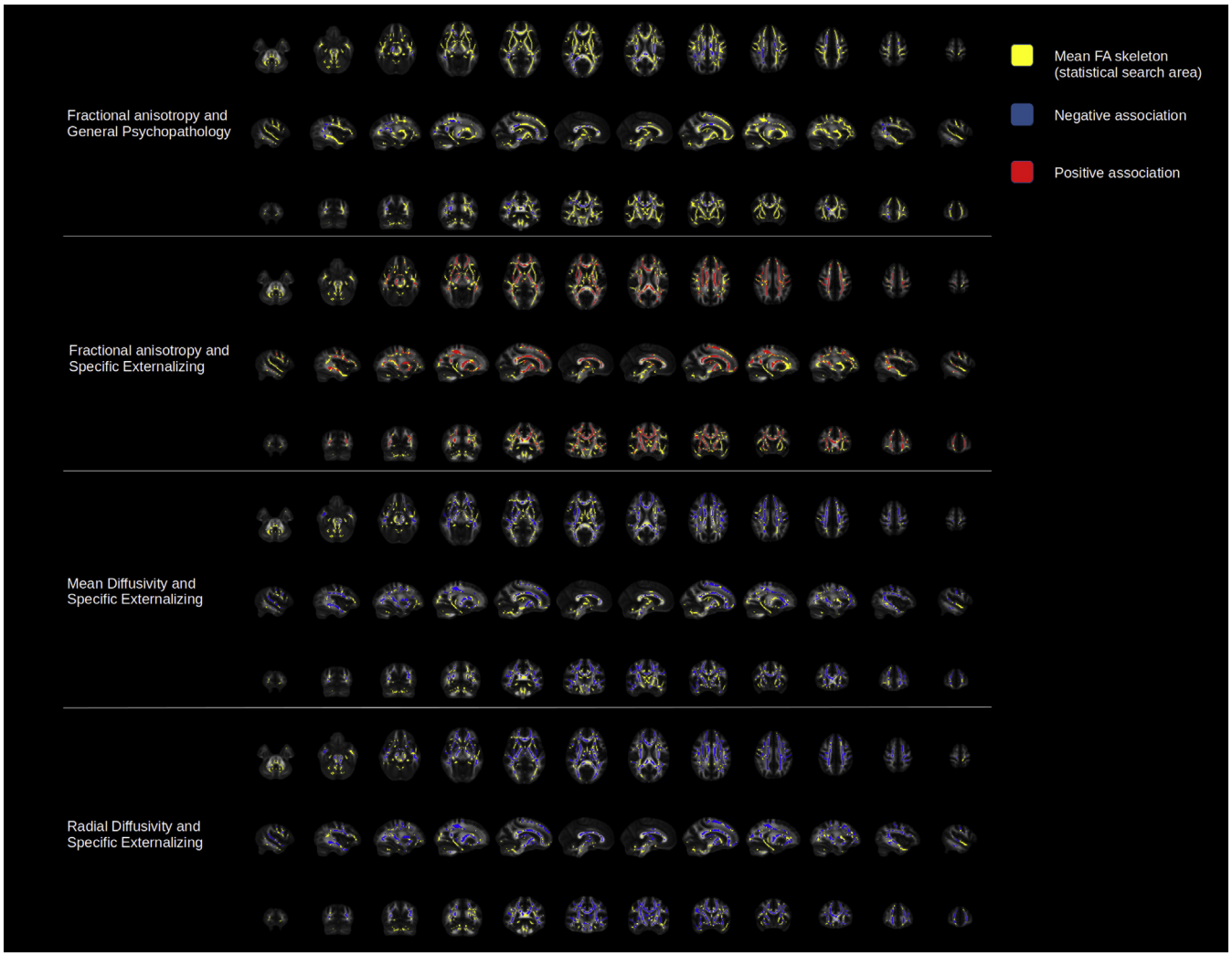
The multi-group analyses showed that the global white matter, general and specific psychopathology constructs and associations did not differ by ancestry, sex or socioeconomic status (Table S9-S11, available online). The association between global white matter and general psychopathology was more than twice as strong in boys (β=-0.11, SE=0.03, p<0.01) than in girls (β=-0.04, SE=0.03, p=0.17), but the difference was not significant (z-test: p=0.14).

TABLE 3 Psychopathology Factors Regressed on White Matter Microstructure

	Factor															
	General				Specific ext				Specific int				Specific att			
Model Name	**β**	**SE**	***p***	**q**	**β**	**SE**	***p***	**q**	**β**	**SE**	***P***	**q**	**β**	**SE**	***p***	**q**
Global FA (main model)	−0.07	0.02	<.01	<0.01	0.07	0.03	.01	0.02	0.02	0.03	.36	0.48	−0.01	0.02	.77	0.77
Adjusted for: child IQ and parental psychopathology	−0.06	0.02	<.01	0.01	0.07	0.03	<.01	0.01	0.02	0.03	.47	0.60	0.01	0.02	.60	0.60
Adjusted for: child BMI	−0.08	0.02	<.01	<0.01	0.08	0.03	<.01	<.01	0.01	0.03	.70	0.79	−0.01	0.02	.79	0.79
Adjusted for: total intracranial volume and motion	−0.07	0.02	<.01	0.01	0.09	0.03	<.01	<0.01	0.01	0.03	.66	0.66	0.02	0.02	.41	0.55
Global MD	0.01	0.02	.78	0.78	−0.06	0.03	.02	.08	0.01	0.03	.65	0.78	−0.04	0.02	.08	0.16
Global RD	0.03	0.02	.12	0.24	−0.07	0.03	.01	0.04	−0.01	0.03	.80	0.80	−0.02	0.02	.37	0.49
Global AD	−0.04	0.03	.10	0.20	−0.02	0.03	.39	0.39	0.03	0.03	.39	0.39	−0.06	0.03	.03	0.12
3-Factor model	—				Externalizing				Internalizing				Attention			
Global FA	—	—	—	—	0.03	0.01	.04	—	0.02	0.01	.15	—	−0.01	0.02	.59	—
CBCL scores	Total				Externalizing				Internalizing				Attention			
Global FA	−0.02	0.02	.26	—	−0.01	0.02	.71	—	−0.01	0.02	.71	—	−0.04	0.02	.06	—
Global FA (adjusted for total score)	—	—	—	—	0.01	0.01	.31	—	0.02	0.01	.06	—	−0.02	0.01	.12	—

Note: White matter microstructure based on fractional anisotropy, unless otherwise noted. All models are adjusted for sex, age at scan, age at psychopathology assessment, maternal and paternal education, household income and genetic ancestry (n = 3,030). AD = axial diffusivity; Att = attention; β = standardized regression coefficient; BMI = body mass index; Ext = externalizing; FA = fractional anisotropy; Int = internalizing; MD = mean diffusivity; q = false discovery rate–adjusted p values; *RD = radial diffusivity; SE = standard error.*

FIGURE 2 Results of the Tract-Based Spatial Statistics (TBSS) Analysis (n = 2,996)



Note: *Voxels in the mean fractional anisotropy (FA) skeleton (yellow) were associated with the general psychopathology and specific externalizing factor, using the scalars fractional anisotropy, mean diffusivity and radial diffusivity; these analyses were adjusted for sex, age at scan, maternal and paternal education, household income and genetic ancestry. Voxels with significant p values after multiple testing correction were coded as blue, if the direction was negative, and red, if the direction was positive. Please note color figures are available online.*

Replication

FA values of the medial cerebellar peduncle showed a negative association with general psychopathology (β=-0.05SD, SE=0.02, p=0.03), of which 25% was shared with global white matter effects. The associations of the pons and lemniscus could not be replicated (Table S12, available online).

DISCUSSION

The results suggest that children with a lower global white matter microstructure had higher levels of general psychopathology. In contrast, more global white matter microstructure was associated with higher levels of the specific externalizing factor. We also found a positive association with the traditionally defined externalizing factor. Our finding were not driven by a single white matter tract, but by white matter differences across the brain.

At age 10 years, the development of many white matter tracts, such as projections of the prefrontal cortex, is still ongoing.[44,45] An altered maturation of white matter microstructure, both delayed or accelerated, at this age might thus be responsible for various psychological problems, ranging from cognitive to behavioral and emotional problems. Lower global white matter microstructure was associated with lower cognition in childhood,[15] and in another study global white matter values were negatively associated with depression.[19] Also, white matter

microstructure is highly heritable in younger ages, with heritability estimates in adolescence exceeding those of adulthood.[46] Genetic variants underlying psychopathology potentially influence psychiatric problems by altering white matter microstructure. However, differences in white matter are not only genetically driven. For instance, children in foster care and children who remained institutionalized show differences in microstructure, suggesting environmental effects.[47] White matter microstructure is thus an indicator for developmental and environmental adversities that underlie psychological problems, or white matter may even mediate these environmental risk effects. The findings implicate that children with a psychiatric problem in one domain, not only are more likely to have psychological problems in another, but are also more likely to have lower white matter microstructure. The negative association of global white matter microstructure with general psychopathology supports the notion that lower white matter microstructure is a marker for poorer mental health and IQ. FA is a non-specific measure of white matter integrity and related to "axonal count and density, degree of myelination and fiber organization."[48] As FA showed a stronger association than RD or AD alone, this may indicate that the absolute magnitude of diffusion along or perpendicular to the axon is not as important as the interplay between both. In other words, higher radial diffusivity in relation to a given amount of axial diffusivity associates with general psychopathology, rather than the absolute magnitude. The observed associations between global white matter and general psychopathology suggest that the impact of any change in white matter structure may not be limited to a specific psychopathology, or the reverse, the assumption that behavioral changes likely affect the development of specific brain areas only, may be too simplistic.

Lower FA values, however, are not found in all psychiatric disorders. Higher dorsal white matter microstructure ("where pathway") is associated with more visuospatial deficits in Williams syndrome,[49] and developmental increases of FA were associated with lower IQ levels depending on sex and brain region.[50] Furthermore, ADHD is inconsistently associated with higher white matter microstructure in some regions.[17] At first glance, the contrasting positive association with the specific externalizing factor suggests that higher white matter microstructure is a specific risk factor for aggressive and rule-breaking behavior in childhood. However, it should be emphasized that the interpretation of the specific factor is different from traditional internalizing/externalizing factors or broadband scales. The traditional factors represent a mixture of general and specific effects and were not associated with white matter microstructure or, as in the case of the externalizing factor, only modestly. The specific factors represent the variance that is not shared with any other problem domains. Compared to the traditional externalizing factor, the specific externalizing factor was associated less negatively with poor school performance and more positively with surgency in this study, characteristics that are not usually positively associated with psychopathology. This may suggest that when accounting for general psychopathology, the remaining specific externalizing factor represents behavior or traits that are less indicative of clinical symptoms; rather, the specific externalizing factor might be indicative of, for example, assertive behavior or other personality traits. In particular, surgency was associated with the specific externalizing factor, however, surgency was not associated with global white matter. As we assessed only a few selected temperamental measures and no personality traits, interpreting the positive association between white matter and specific externalizing factor as association with personality is speculative and cannot be explored further in the present study.

Regardless of the interpretation of the specific factor, our results suggest that any psychiatric problem can be partitioned into a component, which is the consequence of general pathways, and a component, which is due to specific pathways. As both factors can have different psychological and biological correlates, it is crucial for etiological research to also model different specific problem dimensions to elucidate the nature of a disorder and the comorbid symptoms. This is especially true if the direction of the associations of specific and general factors with a biological measure, such as white matter, are in the opposite direction. In our study, the lack of an association with some specific components was, to a degree, masked by the negative associations with the general factor. Most previous research has analyzed specific disorders, without taking into account comorbidity or the partitioning of general and specific effects. Our research highlights that it is important to investigate and to understand a disorder's general and specific components both, as they may have different biological mechanisms and consequences. We also cautiously speculate about the clinical consequences of our findings. As individuals with the same symptom level may differ as to what degree their symptoms reflect general or specific factors, a stronger focus on assessment of comorbid symptoms from different psychopathology domains appears to be warranted. Even if, at first glance, a child displays only a single disorder, other subclinical symptoms need to be assessed carefully, as they can contribute to the underlying biology.

We interpret the associations between white matter microstructure and the psychopathology factors as not

regionally specific based on the following observations. First, the associations of the global white matter variable were either stronger than or at least as strong as any individual tract. This would not be the case if results were driven by a few specific tracts. Second, the direction of the association of the individual tracts with overall or specific psychopathology was consistently that of the global white matter indicator. Third, in the voxelwise TBSS analyses, all individual voxels were associated with the general psychopathology or the specific externalizing factor in the direction predicted by the global model. Although some regions contained more voxels associated with the general psychopathology factor than others, for example, left inferior longitudinal fasciculus and left corticospinal tract (general psychopathology) and forceps minor (specific externalizing), nearly all voxels formed a single continuous cluster spread across the whole brain.

Few neurobiological studies have attempted to distinguish general and specific effects of psychopathological dimensions. Traditional analyses relying on symptom counts or diagnoses of internalizing or externalizing problems typically only estimate the overall association with a single domain. In these studies, it is difficult to disentangle whether the association applies to other psychological domains and whether it is specific to the studied domain. The observation that associations are stronger when partitioning psychopathology into general and specific effects highlights the usefulness of bifactor models, arguably justifying the increase of functional complexity.[51]

That said, a few studies have demonstrated associations with traditional sum-scores or case definitions. In the case of internalizing and attention sum-scores, such an association was only observed only in children born preterm,[20] so the lack of findings in our general population sample is consistent. Lower global white matter was also associated with a higher chance of major depression diagnosis or classification in a previous study.[19] As the children in our study are young and the prevalence of major depression is low, we could not examine the association between white matter and major depression. However, we replicated a tract previously identified to be associated with general psychopathology.[21] We found an association of the white matter integrity of the medial cerebellar peduncle with higher general psychopathology consistent with the most seminal prior imaging study. The pons and lemniscus, however, were not associated with the general psychopathology factor.

In general, longitudinal studies are needed to investigate how general psychopathology and its neurobiological correlates change throughout life. General psychopathology appears to have similar explanatory power in childhood, adolescence, and adulthood, explaining more variance than specific factors at each age.[11,52] Interestingly, this stability may be the result of highly dynamic processes, in which general psychopathology predicts the development of specific psychopathology in one domain. However, this onset of specific psychopathology appears to predict later psychopathology in other domains, resulting in a net stability of general psychopathology over time.[52] These dynamic processes may also be reflected in changes in white matter in that, over time, the negative association of white matter integrity and general psychopathology remains stable, but there may be temporary changes corresponding to specific psychopathology manifestations. This hypothesis needs to be tested in a longitudinal design with repeated white matter and psychopathology assessments.

A strength of our study is the use of latent variables and multiple informants, instruments, and time-points. We compared our results from psychopathology factor models to maternally rated CBCL sum-scores. The association between white matter and CBCL sum-scores were much weaker and nonsignificant compared to the traditional factor model without the general psychopathology factor. We also attempted to mimic the specific factors in regression analyses. Here we controlled externalizing, internalizing, and attention sum-scores for the CBCL total problem score, but the associations remained nonsignificant. This suggest that the combination of multiple informants and time points improves power by reducing measurement error, and that latent variables help in partitioning general and specific variance. The results of latent variables should be more generalizable than traditional regression analysis, as the outcomes tested are not scores of a particular instrument but rather of the underlying constructs. Additional study characteristics contributing to generalizability are the ethnic diversity of the sample and the stringent adjustment for many potential socioeconomic confounders. However, as with any observational study, residual confounding cannot be ruled out. For example, we could not control for verbal IQ. As the Rotterdam population has large ethnic diversity, linguistic IQ measures at young ages tend to measure ethnicity more than linguistic ability. Another challenge to the causal interpretation of our findings is that directionality cannot be established with this study. We assumed that white matter microstructure changes underlie the development of psychopathology. It is, of course, theoretically plausible that changes in white matter structure are either a cause or outcome of psychological problems, or both. Irrespective of the direction, the effect sizes of the global white matter factors were very modest, independently explaining less than 1% of the psychopathology factor variances. To illustrate the effect size in term of predicted score changes, we present the expected changes in mother-rated aggression scores at age 6 years: in children

with 1-SD lower global white matter, the scores are predicted to be 0.21 scores higher because of general psychopathology. The low explained variance may reflect the difficulty in reliably estimating childhood psychopathology, but also the difficulties of estimating global white matter. However, none of the other tested predictors particularly stood out in terms in explanatory power, when carefully controlled for the same variables. This suggests that a multitude of factors need to be examined, if one wishes to reliably predict levels of psychopathology in the general population. Global white matter is but one brain feature that, additively with other neurobiological variables, can explain psychopathology.

In summary, global white matter microstructure was associated with lower general psychopathology in school-aged children. At the same time, higher microstructure was associated with a higher risk for specific externalizing behavior, perhaps better characterized as another trait, for example, assertiveness. Both associations were independent of socioeconomic status and IQ of the child. This study highlights the importance of distinguishing global measures from specific features for both neurobiological substrates as well as psychiatric symptoms. Pediatric brain imaging studies must carefully control for general psychopathology or psychiatric comorbidity to reliably detect any specific white matter microstructural associations. The global effects identified in childhood emphasize the need for early prevention and promotion of brain and mental health. Further studies are needed to replicate these findings and to investigate the temporal direction of association.

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